Influence of Age Ranges on Relationship of Complex Aortic Plaque With Cervicocephalic Atherosclerosis in Ischemic Stroke

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Background: Complex aortic plaque is a potential cause of acute ischemic cerebrovascular disease, which needs timely identification. Also as a marker for systemic atherosclerosis, complex aortic plaque may be indicated by significant (≥50%) cervicocephalic atherosclerotic stenosis. We aimed at examining whether age ranges would influence their association to more accurately estimate the risk of having complex aortic plaque in acute ischemic cerebrovascular disease. *Methods:* Aortic arch and cervicocephalic arteries were simultaneously evaluated using computed tomography angiography. Middle-aged (45-64 years) and old-aged (65-85 years) acute ischemic cerebrovascular disease patients were divided into 2 groups according to whether there was an aortic arch plaque with thickness of greater than or equal to 4 mm or associated ulcerations or mural thrombus. *Results:* Old-aged patients (n = 107) had a higher prevalence of complex aortic plaque (67.3% versus 30.9%, $P < .001$) than those middle aged (n = 178). Among middle-aged patients, the presence of extracranial significant atherosclerotic stenosis (adjusted odd ratio = 2.89, 95% confidence interval: 1.42-5.86) rather than intracranial ones independently predicted complex aortic plaque. Regarding the extent of significant cervicocephalic atherosclerotic stenosis, the presence of multi-segment, bilateral, simultaneous extracranial and intracranial, and simultaneous anterior and posterior circulation ones were independent indicators for complex aortic plaque in the middle-aged subgroup (adjusted odd ratio = 2.42, 2.05, 2.26, 2.14, respectively). By contrast, no statistical correlation of complex aortic plaque and significant cervicocephalic atherosclerotic stenosis was found among old-aged patients. *Conclusion*: Considering the ranges of age was important to more precisely predict complex aortic plaque with significant cervicocephalic atherosclerotic stenosis in acute ischemic cerebrovascular disease.

Key Words: Complex aortic plaque—significant cervicocephalic atherosclerotic stenosis—age ranges—acute ischemic cerebrovascular disease—relationship

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Introduction

Complex aortic plaque (CAP) usually refers to an aortic arch plaque with thickness of greater than or equal to 4 mm, ulcerations, or mural thrombus.[1] It presents in 14%-31% of patients with acute ischemic cerebrovascular disease (AICVD), significantly related to the occurrence and recurrence of AICVD.[2-4] Early recognition of the insidious CAP among patients with AICVD is helpful to identify the precise etiology, evaluate the overall vascular risk, and optimize the clinical management.

CAP is not only an important source of cerebral embolism, but also a marker of systemic atherosclerosis. It was recommended to always consider the possibility of aortogenic embolism in AICVD patients with severe carotid stenosis.[4,5] Given that the direct examination of aortic arch is not commonly accessible, the significant (≥50%) cervicocephalic atherosclerotic stenosis (SCAS), which is routinely assessed in AICVD, may be utilized to select the high-risk patients who need further workup for CAP.

Previous researchers mainly sought to predict CAP with the severity of carotid atherosclerosis by ultrasound in AICVD patients.[6-8] And its indicative value was postulated to be greater among older patients with AICVD, as increases of age could independently raise the risk of having CAP.[9] However, several studies on ischemic stroke patients more than 60 years of age demonstrated no obvious association between the presence of CAP and severe carotid stenosis.[2,3] How on earth does age influence the relationship of CAP with SCAS in AICVD?

Age can exert profound but distinct impacts on the atherosclerotic manifestations of different large arteries.[10,11] Pathologic study revealed that aortic arch plaques generally develop earlier than cervicocephalic arterial plaques,[12] though both of them progress with age.[13] But it was still unclear whether the predictive value of SCAS characteristics for the presence of CAP would vary with ranges of age in AICVD. With this knowledge, the risk of having CAP for AICVD patients might be more accurately estimated.

Computed tomography angiography (CTA) is a noninvasive, reliable, and convenient method to simultaneously evaluate the presence of CAP and the location and extent of SCAS.[14,15] With CTA of aortic arch and cervicocephalic arteries, we aimed to comprehensively delineate the SCAS characteristics of AICVD patients with CAP, and examine whether the associations between CAP and SCAS differ between middle-aged and old-aged patients with AICVD.

Methods

This is a single-center cross-sectional study. The ethics committee at Xuanwu Hospital approved the study and all participants provided informed consent. Patients admitted to the stroke unit in Xuanwu Hospital from July 01, 2016 to June 30, 2017 were enrolled in this study if they meet the following selection criteria. Patients were eligible if they were 45-85 years of age; diagnosed as acute ischemic stroke or transient ischemic attack; within 14 days after onset of symptoms. Patients with suspected nonatherosclerotic arterial stenosis, such as arterial dissection and vasculitis; cardioembolism or revascularization procedures; poor organ functions or hematologic diseases; and contraindications to CTA (hypersensitivity to iodinated contrast media or renal insufficiency) were excluded.

General characteristics

Demographic information and vascular risk factors (hypertension history, diabetes mellitus history, hypercholesterolemia history, smoking, obesity, previous acute ischemic stroke, coronary artery disease history, and chronic kidney disease history) were recorded during a face-to-face interview. Patient is considered as smoking if they actively smoked within the last 12 months before this hospital admission.[16] Obesity was defined as body mass index greater than or equal to 28 kg/m^2 at the time of admission.[17]

National Institute of Health Stroke Scale was scored to assess the global deficit of the stroke. The Trial of Org 10172 in Acute Stroke Treatment criteria were used for the classification of acute ischemic stroke.[18] In addition, stroke caused by aortic arch atherosclerosis was classified into stroke of large-artery atherosclerosis.[19] All patients underwent standard blood tests, brain magnetic resonance imaging with diffusion-weighted imaging sequence or CT scan, 12-lead electrocardiogram, transthoracic echocardiography within 7 days after admission. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation as the guideline recommended.[20]

CTA of aortic arch and cervicocephalic arteries

CTA were performed with a 64-slice spiral CT (Light Speed, General Electric Company). Data were acquired in a caudocranial direction from the aortic arch to the top of the head, using a helical scanning mode. The amount of contrast material (Ultravist 370 Iodine/mL) was adjusted according to the body mass index of the patient and ranged between 40 and 50 mL. Contrast-agent application was controlled using the bolus-tracking technique in the ascending aorta (signal attenuation threshold, 100 HU). Data acquisition was initiated after threshold was reached in the ascending aorta, with a mean delay of 8 seconds. GE AW4.2 workstation (General Electric Company) was used for data reconstruction and image analysis. Cervicocephalic angiographies were reviewed by a certified radiologist blinded to aortic arch atherosclerosis data. Aortic arch plaques were assessed by another certified radiologist blinded to cervicocephalic atherosclerosis data.

Definition of CAP

The aortic arch was assessed from the aortic root to the distal end of the left subclavian artery.[3] CAP was measured across multiple contiguous, evenly spaced cross sections with regular 5 mm intervals between perpendicular (axial) slices.[21]

CAP was defined as an aortic arch plaque with thickness of greater than or equal to 4 mm or associated ulcerations or mural thrombus.[14] The plaque thickness was measured as the distance from the highest point of the maximal plaque perpendicular to the wall of the outer membrane of the aorta.[22] A defect greater than or equal to 2 mm in depth and width on the plaque surface was considered ulceration.[15]

Characteristics of SCAS

The cervicocephalic arteries were catagorized as extracranial and intracranial segments. The extracranial segments included common carotid, extracranial carotid, extracranial vertebral, and arteries. The intracranial segments included intracranial carotid, intracranial vertebral, basilar, anterior cerebral, middle cerebral, and posterior cerebral arteries. Curved planar reformatting, maximum intensity projection, multiplanar reformatting, and volume rendering images were used to evaluate the cervicocephalic arteries. The percentage of arterial stenosis was quantified on orthogonal views with an automatic vessel analysis tool according to the North American Symptomatic Carotid Endarterectomy Trial method[23] for the extracranial segments and the Warfarin-Aspirin Symptomatic Intracranial Disease Study Trial method[24] for the intracranial segments.

SCAS was defined as cervicocephalic arterial stenosis greater than or equal to 50% or occlusion. Presence of multisegment SCAS, bilateral SCAS, simultaneous extracranial and intracranial SCAS, or simultaneous anterior and posterior circulation SCAS was considered as "diffused SCAS", reflecting the extent of SCAS.

Grouping of study subjects

AICVD patients aged 45-64 years were classified as "middle-aged,"[25] while those 65-85 years of age were categorized as "old-aged."[26] After CTA of aortic arch and cervicocephalic arteries, study subjects were divided into "CAP" and "non-CAP" groups according to whether CAP existed.

Statistical analysis

All statistical tests were performed with the use of SPSS software (v17.0; IBM, Armonk, NY). P value less than .05 was considered statistically significant.

The prevalence of CAP and SCAS characteristics were compared between "middle-aged" and "old-aged" AICVD patients. The general and SCAS characteristics were compared between "CAP" and "non-CAP" groups, respectively among "middle-aged" and "old-aged" AICVD patients. Data were presented as mean ± standard deviation for continuous variables, count (percentage) for dichotomous variables, and median (quartile 25%, quartile 75%) for ordinal variables. Student's t test was used for continuous variable that is normally distributed, Mann-Whitney U test for continuous variable that is not normally distributed and chi-square test for dichotomous variable.

To assess the independent predictive value of SCAS for CAP, each SCAS characteristic was entered into multivariate logistic regression model with statistically significant demographic characteristics and vascular risk factors. The multivariate analysis was respectively performed in "middle-aged" and "old-aged" AICVD patients. Adjusted odds ratios (ORs) for the presence of CAP were calculated with 95% confidence intervals.

Results

Total study population

A total of 319 patients with AICVD were admitted to the stroke unit. Thirteen patients whose symptoms had

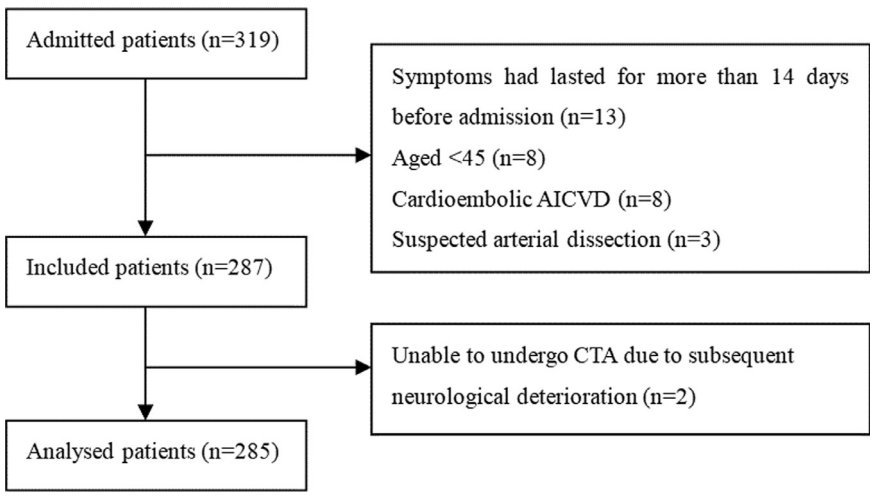

Figure 1. *Flow chart of patients' enrollment.*

Table 1. *General characteristics of middle-aged and old-aged patients with AICVD*

Characteristics	Total (n = 285)	Middle aged (n = 178)	Old aged (n = 107)	*P* value
Male (n, %)	219 (76.8)	143 (80.3)	76 (71.0)	.071
Vascular risk factors				
History of HBP (n, %)	188 (66.0)	114 (64.0)	74 (69.2)	.378
History of DM (n, %)	108 (37.9)	69 (38.8)	39 (36.4)	.696
History of HLP (n, %)	57 (25.2)	30 (16.9)	27 (25.2)	.087
Smoking (n, %)	123 (43.2)	89 (50.0)	34 (31.8)	.003*
Obesity (n, %)	60 (21.1)	44 (24.7)	16 (15.0)	.050
History of AIS (n, %)	84 (29.5)	53 (29.8)	31 (29.0)	.885
History of CAD (n, %)	50 (17.5)	18 (10.1)	32 (29.9)	<.001*
History of CKD (n, %)	0 (0)	0 (0)	0 (0)	-
Clinical findings				
NIHSS on admission [M(Q25, Q75)]	3 (1,6)	3 (1,6)	3 (1,6)	.444
SBP on admission (mmHg, X ± S)	151 ± 22	149 ± 21	154 ± 23	.088
DBP on admission (mmHg, X ± S)	86 ± 12	88 ± 11	82 ± 12	<.001*
AICVD subtype				.760
TIA (n, %)	15 (5.3)	8 (4.5)	7 (6.5)	
Stroke of large-artery atherosclerosis (n, %)	172 (60.4)	110 (61.8)	62 (57.9)	
Stroke of small-vessel occlusion (n, %)	85 (29.8)	51 (28.7)	34 (31.8)	
Cryptogenic stroke (n, %)	13 (4.6)	9 (5.1)	4 (3.7)	
Laboratory findings				
FBG [mmol/L, M(Q25, Q75)]	5.7 (5.1, 7.5)	5.8 (5.1, 7.4)	5.6 (5.0, 7.5)	.521
LDL-C (mmol/L, X ± S)	2.6 ± .9	2.5 ± .9	2.6 ± .9	.450
HDL-C (mmol/L, X ± S)	1.2 ± .3	1.1 ± .3	1.2 ± .3	.037*
Fibrinogen [g/L, M(Q25, Q75)]	3.1 (2.5, 3.6)	3.1 (2.5, 3.6)	3.1 (2.5, 3.7)	.894
D-dimer [mg/L, M(Q25, Q75)]	.5 (.3, 1.0)	.3 (.2, .8)	.9 (.5, 1.0)	<.001*
eGFR [mL/min/1.73 m^2, M(Q25, Q75)]	100.4 (91.2, 107.2)	104.3 (98.0, 110.6)	93.0 (85.7, 97.8)	<.001*
LVEF (%, X ± S)	63.9 ± 7.2	63.8 ± 7.3	64.0 ± 7.1	.813

Abbreviations: AICVD, acute ischemic cerebrovascular disease; AIS, acute ischemic stroke; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high density lipoprotein cholesterol; HLP, hyperlipidemia; HTN, hypertension; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure; TIA, transient ischemic attack.

**P* less than.05 was considered statistically significant.

lasted for more than 14 days before admission, 8 patients aged less than 45 years, 8 patients who had cardioembolic AICVD, and 3 patients with suspected arterial dissection were not eligible. Among the 287 included patients, 2 patients could not finish the CTA examination because of subsequent neurological deterioration. Finally 285 patients were involved in the analysis (Fig 1).

The study subjects (270 acute ischemic stroke and 15 transient ischemic attack) were 62.0 ± 9.3 years of age on average (minimum 45 years, median 61 years, and

Table 2. *CAP and SCAS characteristics of middle-aged and old-aged AICVD patients*

Characteristics	Total (n = 285)	Middle aged (n = 178)	Old aged (n = 107)	*P* value
Presence of CAP	127 (44.6)	55 (30.9)	72 (67.3)	<.001*
Presence of SCAS	221 (77.5)	129 (72.5)	92 (86.0)	.008*
Extracranial SCAS	115 (40.4)	63 (35.4)	52 (48.6)	.028*
Intracranial SCAS	198 (69.5)	117 (65.7)	81 (75.7)	.077
Diffused SCAS	173 (60.7)	95 (53.4)	78 (72.9)	.001*
Multi-segment SCAS	169 (59.3)	93 (52.2)	76 (71.0)	.002*
Bilateral SCAS	151 (53.0)	83 (46.6)	68 (63.6)	.006*
Simultaneous extracranial and intracranial SCAS	92 (32.3)	51 (28.7)	41 (38.3)	.091
Simultaneous anterior and posterior circulation SCAS	116 (40.7)	63 (35.4)	53 (49.5)	.019*

Data was displayed as number (percentage).

Abbreviations: AICVD, acute ischemic cerebrovascular disease; CAP, complex aortic plaque; SCAS, significant (≥50%) cervicocephalic atherosclerotic stenosis.

**P* value less than.05 was considered statistically significant.

Table 3. *General characteristics of middle-aged and old-aged AICVD patients with CAP*

Characteristics	Total			Middle aged			Old aged		
	CAP (n = 127)	Non-CAP (n = 158)	*P* value	CAP (n = 55)	Non-CAP (n = 123)	*P* value	CAP (n = 72)	Non-CAP (n = 35)	*P* value
Age (year, X ± S)	66.1 ± 9.0	58.7 ± 8.2	<.001*	57.7 ± 5.1	55.3 ± 5.0	.986	72.5 ± 5.3	70.8 ± 5.4	.845
Male (n, %)	98 (77.2)	121 (76.6)	.908	50 (90.9)	93 (75.6)	.018*	48 (66.7)	28 (80.0)	.154
Vascular risk factors									
History of HBP (n, %)	96 (75.6)	92 (58.2)	.002*	40 (72.7)	74 (60.2)	.106	56 (77.8)	18 (51.4)	.006*
History of DM (n, %)	57 (44.9)	51 (32.3)	.029*	27 (49.1)	42 (34.1)	.059	30 (41.7)	9 (25.7)	.108
History of HLP (n, %)	32 (25.2)	25 (15.8)	.049*	10 (18.2)	20 (16.3)	.752	22 (30.6)	5 (14.3)	.752
Smoking (n, %)	59 (46.5)	64 (40.5)	.313	34 (61.8)	55 (44.7)	.035*	25 (34.7)	9 (25.7)	.348
Obesity (n, %)	22 (17.3)	38 (24.1)	.166	10 (18.2)	34 (27.6)	.176	12 (16.7)	4 (11.4)	.476
History of AIS (n, %)	43 (33.9)	41 (25.9)	.146	22 (40.0)	31 (25.2)	.046*	21 (29.2)	10 (28.6)	.949
History of CAD (n, %)	33 (26.0)	17 (10.8)	.001*	7 (12.7)	11 (8.9)	.439	26 (36.1)	6 (17.1)	.044*
History of CKD (n, %)	0 (0)	0 (0)	-	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Clinical findings									
NIHSS on admission [M(Q25, Q75)]	3 (1, 5)	3 (1, 7)	.024*	3 (1, 6)	3 (1, 7)	.670	2.5 (1, 4)	5 (2, 8)	.003*
SBP on admission (mmHg, X ± S)	162 ± 22	149 ± 21	.020*	153 ± 20	148 ± 21	.571	155 ± 24	151 ± 22	.878
DBP on admission (mmHg, X ± S)	85 ± 13	87 ± 11	.703	89 ± 13	87 ± 11	.718	81 ± 12	84 ± 12	.626
AICVD subtype			.003*			.001*			.003*
TIA (n, %)	6 (3.8)	9 (7.1)	.216	6 (4.9)	2 (3.6)	.712	0 (.0)	7 (9.7)	.136
Stroke of large-artery atherosclerosis (n, %)	84 (53.2)	88 (69.3)	.006†	65 (52.8)	45 (81.8)	<.001†	19 (54.3)	43 (59.7)	.593
Stroke of small-vessel occlusion (n, %)	57 (36.1)	28 (22.0)	.010†	45 (36.6)	6 (10.9)	<.001†	12 (34.3)	22 (30.6)	.697
Cryptogenic stroke (n, %)	11 (7)	2 (1.6)	.030	7 (5.7)	2 (3.6)	.835	4 (11.4)	0 (.0)	.017
Laboratory findings									
FBG [mmol/L, M(Q25, Q75)]	5.9 (5.1, 7.5)	5.6 (5.1, 7.3)	.419	5.7 (5.1,7.1)	5.5 (5.0, 6.7)	.235	5.6 (5.0, 7.5)	5.6 (4.9, 7.8)	.759
LDL-C (mmol/L, X ± S)	2.6 ± .9	2.5 ± .9	.350	2.6 ± 1.0	2.4 ± .8	.104	2.6 ± .9	2.7 ± .9	.320
HDL-C (mmol/L, X ± S)	1.2 ± .3	1.2 ± .3	.838	1.1 ± .3	1.1 ± .3	.821	1.2 ± .7	1.3 ± .3	.154
Fibrinogen [g/L, M(Q25, Q75)]	3.1 (2.5, 3.7)	3.1 (2.5, 3.6)	.413	3.3 (2.6, 3.7)	3.1 (2.5, 3.6)	.283	3.0 (2.5, 3.8)	3.2 (2.4, 3.9)	.994
D-dimer [mg/L, M(Q25, Q75)]	.7 (.3, 1.0)	.4 (.2, .9)	.001*	.4 (.2,1.0)	.3 (.2, .8)	.179	.9 (.5, 1.1)	.6 (.4, 1.0)	.352
eGFR [mL/min/1.73m^2, M(Q25, Q75)]	102.9 (96.3, 109.5)	95.2 (86.6, 103.3)	<.001*	105.0 (99.9, 110.9)	101.5 (93.5, 109.5)	.058	95.0 (89.0, 99.9)	89.5 (84.9, 97.7)	.082
LVEF (%, X ± S)	64.0 ± 7.6	63.8 ± 6.8	.844	63.5 ± 8.0	64.5 ± 5.6	.468	65.4 ± 6.2	63.3 ± 7.5	.168

Abbreviations: AICVD, acute ischemic cerebrovascular disease; AIS, acute ischemic stroke; CAD, coronary artery disease; CAP, complex aortic plaque; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HTN, hypertension; HDL-C, high density lipoprotein cholesterol; HLP, hyperlipidemia; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure; TIA, transient ischemic attack.

*P less than .05 was considered statistically significant.

†P less than .0125 (.05/4) was considered statistically significant for multiple test correction.

maximum 84 years), with predominant males (76.8%) (Table 1). CAP was detected in 127/285 (44.6%), while 221/285 (77.5%) patients had SCAS and the diffused SCAS was found in 173/285 (60.7%) (Table 2).

Characteristics of middle-aged and old-aged AICVD patients

There were 178 (62.5%) patients middle aged and the remaining 107 (37.5%) patients were old aged. The old-aged AICVD patients had a higher prevalence of CAP (67.3% versus 30.9%, $P < .001$), SCAS (86.0% versus 72.5%, $P = .008$), and diffused SCAS (72.9% versus 53.4%, $P = .001$) than those middle aged (Table 2). The comparisons of general characteristics between the 2 age-subgroups were shown in Table 1. Specially, compared to the middle-aged patients, those old aged tended to have a history of coronary artery disease, but the left ventricular ejection fraction was not obviously lower. Although none of the patients had a history of chronic kidney disease, patients in the old-age subgroup had significantly lower estimated glomerular filtration rate than those in the middle-age subgroup. The AICVD subtype was similar between the 2 age-subgroups. Among 172 patients with stroke of large-artery atherosclerosis, CAP was more frequent detected in the old-age subgroup than in the middle-age subgroup [43/62 (69.4%) versus 45/110 (40.9%), $P < .001$].

General characteristics of AICVD patients with CAP

Among the middle-aged patients, those in CAP group were more likely to be male (90.0% versus 75.6%, $P = .018$), on smoking (61.8% versus 44.7%, $P = .035$), positive in acute ischemic stroke history (40.0% versus 25.2%, $P = .046$), suffering stroke of large-artery atherosclerosis (81.8% versus 52.8%, $P < .001$), and were less likely to have stroke of small-vessel occlusion (10.9% versus 36.6%, $P < .001$) than those in non-CAP group. The age and other general characteristics were not significantly different between the 2 groups.

Among the old-aged patients, those with CAP were more frequently have a history of hypertension (77.8% versus 51.4%, $P = .006$) and coronary artery disease (36.1% versus 17.1%, $P = .044$) in comparison to patients without CAP. The age, AICVD subtype, and other general characteristics were similar between patients with and without CAP (Table 3).

SCAS characteristics of AICVD patients with CAP

In the middle-aged subgroup, patients with CAP were more likely to have extracranial SCAS (56.4% versus 26.0%, $P < .001$) than those without CAP, but the prevalence of intracranial SCAS was not significantly different in between. Regarding the extent, multi-segment SCAS (69.1% versus 44.7%, $P = .003$), bilateral SCAS (60.0% versus40.7%, $P = .017$), simultaneous extracranial and intracranial SCAS (45.5% versus 21.1%, $P = .001$), and

Table 4. *SCAS characteristics of middle-aged and old-aged AICVD patients with CAP*

Characteristics	Total			Middle aged			Old aged		
	CAP (n = 127)	Non-CAP (n = 158)	*P* value	CAP (n = 55)	Non-CAP (n = 123)	*P* value	CAP (n = 72)	Non-CAP (n = 35)	*P* value
Extracranial SCAS	70 (55.1)	45 (28.5)	<.001*	31 (56.4)	32 (26.0)	<.001*	39 (54.2)	13 (37.1)	.098
Intracranial SCAS	90 (70.9)	108 (68.4)	.647	39 (70.9)	78 (63.4)	.330	51 (70.8)	30 (85.7)	.092
Extent of SCAS									
Multi-segment SCAS	88 (69.3)	81 (51.3)	.002*	38 (69.1)	55 (44.7)	.003*	50 (69.4)	26 (74.3)	.605
Bilateral SCAS	76 (59.8)	75 (47.5)	.037*	33 (60.0)	50 (40.7)	.017*	43 (59.7)	25 (71.4)	.238
Simultaneous extracranial and intracranial SCAS	54 (42.5)	38 (24.1)	.001*	25 (45.5)	26 (21.1)	.001*	29 (40.3)	12 (34.3)	.550
Simultaneous anterior and posterior circulation SCAS	62 (48.8)	54 (34.2)	.012*	27 (49.1)	36 (29.3)	.011*	35 (48.6)	18 (51.4)	.784

Data was displayed as number (percentage).

Abbreviations: AICVD, acute ischemic cerebrovascular disease; CAP, complex aortic plaque; SCAS, significant (≥50%) cervicocephalic atherosclerotic stenosis.

*P value less than .05 was considered statistically significant.

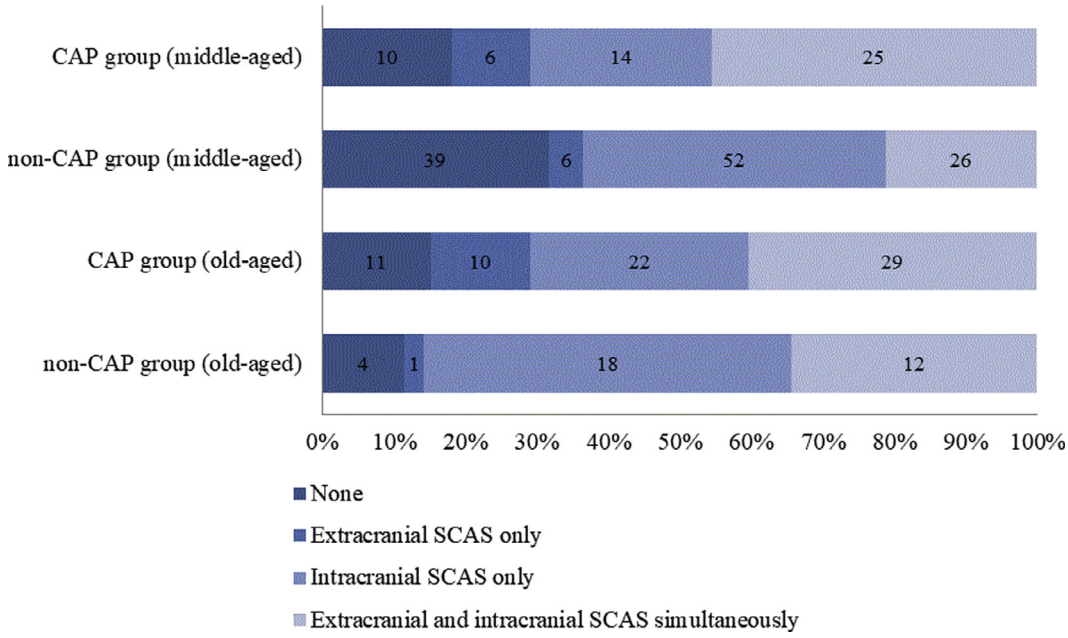

Figure 2. *Distribution of SCAS in extracranial and intracranial arteries among middle-aged and old-aged AICVD patients with and without CAP.* Abbreviations: *AICVD, acute ischemic cerebrovascular disease; CAP, complex aortic plaque; SCAS, significant (≥50%) cervicocephalic atherosclerotic stenosis.*

simultaneous anterior and posterior circulation SCAS (49.1% versus 29.3%, $P = .011$) were all more frequent among patients with CAP.

In contrast, among the old-aged patients, the prevalence of extracranial and intracranial SCAS, and the extent characteristics of SCAS were similar between patients with and without CAP (Table 4 and Figure 2).

Indicative value of SCAS characteristics for CAP in AICVD

In the middle-aged subgroup, the presence of extracranial SCAS and diffused SCAS were associated with higher likelihood to have CAP (Table 5). After adjustment for age, sex, and vascular risk factors, the OR (95% confidence interval) of extracranial SCAS, multisegment SCAS, bilateral SCAS, simultaneous extracranial and intracranial SCAS, and simultaneous anterior and posterior circulation SCAS for the presence of CAP were 2.89 (1.42-5.86), 2.42 (1.18-4.93), 2.05 (1.02-4.13), 2.26 (1.09-4.70), and 2.14 (1.06-4.31) in respective (Table 6).

Among the old-aged patients, the presence of extracranial or intracranial SCAS, as well as various extent characteristics of SCAS, was not related to the risk of having CAP, with or without adjustment for age, sex, and vascular risk factors (Table 5, Table 7).

Discussion

With CTA of aortic arch and cervicocephalic arteries in AICVD patients 45-85 years of age, this study demonstrated that the extracranial SCAS and the extent characteristics of SCAS were independent indicators for the presence of CAP among middle-aged (45-64years) AICVD patients. Notwithstanding that the old-aged (65-85years) AICVD patients were more likely to have CAP, SCAS, and diffused SCAS than those middle-aged, no statistical correlation of CAP and SCAS characteristics was found in the old-aged subgroup.

The prevalence of CAP in this CTA study was higher than prior transesophageal echocardiography (TEE) data (44.6% versus 24%-31%[27-29]). It might be because we only enrolled patients more than 45 years of age, the noninvasive and easy-cooperating features of CTA reduced the selection bias inherent in TEE studies of CAP,[30] and CTA could image the aortic arch more completely and detect the plaque ulcerations more sensitively in comparison to TEE.[31]

In this study, the middle-aged patients had generally lighter burden of atherosclerosis in both aortic arch and cervicocephalic arteries than those old aged, consistent with previous researches.[13,27,29] More importantly, our data for the first time showed that the predictive value of SCAS for CAP might be greater among middle-aged AICVD patients in comparison with that among old-aged AICVD patients.

For individuals predisposed to atherosclerosis, the atherosclerotic lesions generally appear earlier in the aorta than in the cervicocephalic arteries.[12] The presence of SCAS might suggest that the aortic arch plaques have developed into an advanced stage, so the presence and extent of SCAS could serve as predictors for the presence of CAP. However, as shown in this study, the statistically significant associations between SCAS and CAP among the middle-aged AICVD patients mainly derived from the "double negative" subjects with neither CAP nor each SCAS characteristic. With the increase of age, more aortic

arch plaques evolved into CAP and more cervicocephalic atherosclerotic lesions became SCAS or diffused SCAS. As a consequence, the proportion of "double negative" subjects notably reduced among the old-aged AICVD patients. But only a part of them turned into the "double positive" ones, and the others were merely "single positive". Though some "single positive" patients might also progress into the "double negative" ones, we found the ratio of "single positive" AICVD patients increased (Table 8). Just the "double negative" and "double positive" ones would contribute to a closer statistical association between CAP and SCAS, while the "single positive" ones would influence oppositely. Thus, the predictive value of SCAS characteristics for the presence of CAP could be remarkable among middle-aged AICVD patients, but not significant among those old aged.

A lack of association between CAP and severe carotid stenosis among the elderly ischemic stroke patients had been observed before. In an autopsy study, where 163/183 (89.0%) of the study subjects were greater than or equal to 60 years of age, Amarenco et al[32] found that cerebral infarction patients with and without carotid greater than or equal to 75% stenosis had similar frequency of aortic arch ulcerated plaques (data not given). A subsequent TEE study targeting ischemic stroke patients aged greater than or equal to 60 years manifested that aortic arch plaque greater than or equal to 4 mm in thickness was equally frequent in patients with carotid greater than or equal to 70% stenosis, patients with carotid less than 70% stenosis, and patients with no stenosis (15%, 15%, and 14%, $P = .9$).[2]

In our study, both the presence and the extent of SCAS were used to delineate the SCAS conditions, offering a more complete picture for the associations between CAP and SCAS. Consequently, above differences detected between the 2 age-subgroups might be a more reliable reflection of the differential impacts of age ranges on the relationship of CAP with SCAS. And these data provided the first evidence that both the presence and the extent of SCAS were important characteristics to predict the concomitant CAP of AICVD patients. Moreover, we found that extracranial SCAS possibly be more potent than intracranial SCAS in estimating the risk of having CAP. Although no research had directly addressed this issue, an autopsy study on general population aged 35-69 years showed that atherosclerotic area of aorta paralleled those of carotid arteries rather than those of intracranial arteries.[33]

Taken together, this study suggested that atherosclerotic manifestations of aortic arch and cervicocephalic arteries might have multifaceted and age-dependent interconnections. Among middle-aged AICVD patients, the risk of having CAP was relatively high if either extracranial SCAS or diffused SCAS existed. However, among old-aged AICVD patients, CAP was more prevalent but less predictable by SCAS characteristics. The high

Table 5. *Frequency of CAP in AICVD patients with various SCAS characteristics*

Characteristics	Total			Middle aged			Old aged		
	Yes	No	*P* value	Yes	No	*P* value	Yes	No	*P* value
Extracranial SCAS	70/115 (60.9)	57/170 (33.5)	<.001*	31/63 (49.2)	24/115 (20.9)	<.001*	39/52 (75.0)	33/55 (60.0)	.098
Intracranial SCAS	90/198 (45.5)	37/87 (42.5)	.647	39/117 (33.3)	16/61 (26.2)	.330	51/81 (63.0)	21/26 (80.8)	.092
Extent of SCAS									
Multi-segment SCAS	88/169 (52.1)	39/116 (33.6)	.002*	38/93 (40.9)	17/85 (20.0)	.003*	50/76 (65.8)	22/31 (71.0)	.605
Bilateral SCAS	76/151 (50.3)	51/134 (38.1)	.037*	33/83 (39.8)	22/95 (23.2)	.017*	43/68 (63.2)	29/39 (74.4)	.238
Simultaneous extracranial and intracranial SCAS	54/92 (58.7)	73/193 (37.8)	.001*	25/51 (49.0)	30/127 (23.6)	.001*	29/41 (70.7)	43/66 (65.2)	.550
Simultaneous anterior and posterior circulation SCAS	62/116 (53.4)	65/169 (38.5)	.012*	27/63 (42.9)	28/115 (24.3)	.011*	35/53 (66.0)	37/54 (68.5)	.784

Data was displayed as number/total number (percentage).

Abbreviations: AICVD, acute ischemic cerebrovascular disease; CAP, complex aortic plaque; SCAS, significant (≥50%) cervicocephalic atherosclerotic stenosis.

*P value less than .05 was considered statistically significant.

Table 6. *Indicative value of SCAS characteristics for CAP in middle-aged AICVD patients*

Characteristics	Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value
Extracranial SCAS	3.67 (1.89-7.16)	<.001	2.89 (1.42-5.86)	.003*
Intracranial SCAS	1.41 (.71-2.80)	.331	1.22 (.58-2.56)	.607
Extent of SCAS				
Multi-segment SCAS	2.76 (1.41-5.42)	.003	2.42 (1.18-4.93)	.015*
Bilateral SCAS	2.19 (1.15-4.19)	.018	2.05 (1.02-4.13)	.043*
Simultaneous extracranial and intracranial SCAS	3.11 (1.57-6.17)	.001	2.26 (1.09-4.70)	.029*
Simultaneous anterior and posterior circulation SCAS	2.33 (1.21-4.49)	.011	2.14 (1.06-4.31)	.033*

Univariate and multivariate Logistic regression analysis were used. *P* value less than .05 was considered statistically significant.

Abbreviations: AICVD, acute ischemic cerebrovascular disease; CAP, complex aortic plaque; CI, confidence interval; OR, odds ratio; SCAS, significant (≥50%) cervicocephalic atherosclerotic stenosis.

*SCAS characteristics independently related to concomitant CAP after adjustment of age, sex, and significantly different vascular risk factors in univariate analysis (smoking and acute ischemic stroke history).

Table 7. *Indicative value of SCAS characteristics for CAP in old-aged AICVD patients*

Characteristics	Crude OR (95%CI)	*P* value	Adjusted OR* (95%CI)	*P* value
Extracranial SCAS	2.00 (.87-4.58)	.101	2.11 (.85-5.20)	.106
Intracranial SCAS	.41 (.14-1.19)	.099	.51 (.16-1.64)	.257
Extent of SCAS		.		
Multi-segment SCAS	.79 (.32-1.95)	.605	.88 (.32-2.39)	.799
Bilateral SCAS	.59 (.25-1.42)	.240	.69 (.23-1.59)	.302
Simultaneous extracranial and intracranial SCAS	1.29 (.56-3.00)	.550	1.50 (.60-3.77)	.388
Simultaneous anterior and posterior circulation SCAS	.89 (.40-2.00)	.785	.92 (.38-2.24)	.861

Univariate and multivariate Logistic regression analysis were used. *P* value less than .05 was considered statistically significant.

Abbreviations: AICVD, acute ischemic cerebrovascular disease; CAP, complex aortic plaque; CI, confidence interval; OR, odds ratio; SCAS, significant (≥50%) cervicocephalic atherosclerotic stenosis.

*OR after adjustment of age, sex, and significantly different vascular risk factors in univariate analysis (history of hypertension and coronary artery disease).

likelihood to have concomitant CAP should be also considered even if old-aged AICVD patients had only mild cervicocephalic atherosclerosis.

Interestingly, while AICVD patients with CAP were significantly older than those without in our total study population, the age was similar between patients with and without CAP in the old-aged subgroup, as well as in the middle-aged subgroup. Therefore, the age-related risk of having CAP might not be continuous and linear, but instead be stage like and increase abruptly when AICVD patients entered into old age. Analyzing the relationship of CAP with SCAS respectively in middle-aged and old-aged AICVD patients might be important to more precisely predict the existence of CAP.

Different ranges of age indicated different prevalence of risk factors and different exposure time to the risk factors.[34] Supposedly, aortic arch and cervicocephalic arteries might have distinct atherosclerotic responses to them, giving rise to a distinct relationship of CAP with SCAS characteristics between middle-aged and old-aged AICVD patients. We preliminarily found that the CAP-related vascular risk factors were different between the 2 age-subgroups: male, smoking and acute ischemic stroke history could increase the risk of having CAP among the middle-aged AICVD patients, whereas history of hypertension and coronary artery disease was in association with the presence of CAP among those old aged. More researches are needed to clarify the detailed interaction between ranges of age and risk factors, and determine its impacts on predicting CAP with SCAS characteristics.

The presence of CAP would increase the risk of recurrent stroke.[3] According to our results, it is not only because CAP serves as a potential source of cerebral embolism, but also in that CAP is an indicator of severe and diffused cervicocephalic atherosclerosis. And the latter is especially true for the middle-aged patients with AICVD. As for determining etiology and pathophysiologic mechanisms of the present AICVD, CAP itself mainly cause AICVD by arterial-to-arterial embolism, whereas SCAS may result in hemodynamic AICVD, with or without generating embolus.[19] The close relationship of CAP and SCAS shown in our study, particularly among middle-aged AICVD patients, highlighted the difficulty in confirming the precise origin of plaque-derived embolus if CAP and possible culprit SCAS coexisted in patients with the stroke of large-artery atherosclerosis. In addition, embolus generated by CAP may exacerbate the post-SCAS blood flow insufficiency when they go pass the severe cervicocephalic

Table 8. *Frequency distribution of SCAS characteristics and CAP in middle-aged and old-aged AICVD patients*

SCAS characteristics	Middle aged (n = 178)			Old aged (n = 107)		
	Double positive*	Single positive†	Double negative‡	Double positive*	Single positive†	Double negative‡
Extracranial SCAS	31 (17.4)	56 (31.5)	91 (51.1)	39 (36.4)	46 (43.0)	22 (20.6)
Intracranial SCAS	39 (21.9)	94 (52.8)	45 (25.3)	51 (47.7)	51 (47.7)	5 (4.7)
Extent of SCAS						
Multi-segment SCAS	38 (21.3)	72 (40.4)	68 (38.2)	50 (46.7)	48 (44.9)	9 (8.4)
Bilateral SCAS	33 (18.5)	72 (40.4)	73 (41.0)	43 (40.2)	54 (50.5)	10 (9.3)
Simultaneous extracranial and intracranial SCAS	25 (14.0)	56 (31.5)	97 (54.5)	29 (27.1)	55 (51.4)	23 (21.5)
Simultaneous anterior and posterior circulation SCAS	27 (15.2)	64 (36.0)	87 (48.9)	35 (32.7)	55 (51.4)	17 (15.9)

Data was displayed as number (percentage).
Abbreviations: AICVD, acute ischemic cerebrovascular disease; CAP, complex aortic plaque; SCAS, significant (≥50%) cervicocephalic atherosclerotic stenosis.
*Double positive indicated AICVD patients with both CAP and each SCAS characteristic.
†Single positive indicated AICVD patients with either CAP or each SCAS characteristic, but not with both of them.
‡Double negative indicated AICVD patients with neither CAP nor each SCAS characteristic.

arterial stenosis, leading to a SCAS-related hemodynamic AICVD. Therefore, sometimes aortogenic AICVD is indistinguishable from AICVD attributed to SCAS. Just like in this study population, all patients with the stroke of large-artery atherosclerosis with CAP also had possible culprit SCAS (data not shown), so we found no definite "aortogenic stroke per se."

There were some limitations with this study. First, the sample size was relatively small, and all the patients were derived from a single senior stroke unit, who generally had serious atherosclerosis. It might undermine the generalizability of our results. Second, CTA was not the golden method to evaluate CAP and SCAS. Some SCAS might not be atherosclerotic but due to other pathologies, even though we prudently excluded the suspected patients. Third, the complexity of aortic arch plaque, as well as the presence and extent of SCAS, represented important but not all atherosclerotic characteristics of these 2 arterial beds. No statistical association of CAP with various SCAS characteristics tested in this study was not equal to a lack of relationship between atherosclerosis of aortic arch and cervicocephalic arteries. Our preliminary results should be validated by larger-scale studies, and more researches are needed to figure out the possible underlying mechanisms. Cohort studies might be designed to investigate the utility of this age-dependent association of CAP with SCAS in ACIVD patients to optimize their etiology determination, risk stratification, and clinical management.

Conclusions

CAP was prevalent in patients with AICVD. The presence and extent of SCAS had significant indicative value for CAP among middle-aged AICVD patients, but not among those old-aged. Ranges of age influenced the relationship of CAP with SCAS in AICVD. It was important to take age ranges into consideration when SCAS characteristics were utilized to estimate the risk of having CAP for AICVD patients.

Conflict of Interest: None.

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